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TITLE: Signal Enchancement Ratios (SERS) in Breast Carcinomas Measured by 3D Contrast-MRI and Verified by Histopathology

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13. ABSTRACT ***(Maximum 200 Words)***

The goal of this study is the evaluation of a three-point contrast-enhanced magnetic resonance imaging (MRI) technique for characterizing breast carcinoma. We have developed a high resolution method that captures both anatomic heterogeneity as well as differences in contrast uptake pattern, using the signal enhancement ratio (SER). Over 400 patients with confirmed or suspected breast cancer have been evaluated using this technique. In an initial comparison of MRI to mammography for defining the extent of disease in the breast, we reported superior capability of MRI relative to mammography, with particular value in cases of multifocal disease or presence of an associated in-situ component. We found a significant correlation between peak SER value and both tumor grade and microvessel density, and demonstrated improved diagnostic specificity of the three-point SER method over a standard two-point 'static' method. We also evaluated the influence of time interval between surgical excision and subsequent MRI in cases of incomplete tumor resection, on the ability to diagnose residual disease. This evaluation led to a recommendation for a 28-day delay to maximize diagnostic accuracy while minimizing delay to re-excision. The characterization studies have led to the application of contrast-MRI to evaluation of treatment response for patients with locally-advanced breast cancer who undergo pre-operative chemotherapy. Our early results suggest that MRI is more accurate than conventional methods (mammography and physical exam) for measuring change with treatment and may provide unique non-invasive markers that can be used to predict response and recurrence.

14. SUBJECT TERMS
Breast Cancer, Magnetic Resonance Imaging (MRI), high resolution, contrast dynamics, histopathology, local staging, angiogenesis

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FINAL REPORT FOR CONTRACT NUMBER DAMD17-96-C-6126

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Principal Investigator: Nola Hylton, Ph.D., University of California, San Francisco

Grant Title: Signal Enhancement Ratios (SERs) in Breast Carcinomas Measured by 3D Contrast-MRI and Verified by Histopathology

INTRODUCTION

Our work in breast MRI has focused on an imaging technique, the **t**riple **a**cquisition **r**apid **g**radient **e**cho **t**echnique (TARGET), and **s**ignal **e**nhancement **r**atio (SER) analysis method, directed toward defining the extent of malignant lesions in patients with confirmed breast carcinoma. We developed a 3-point contrast-MRI method to maximize anatomic (sensitivity) and biologic (specificity) information in a single exam. Previously reported methods have relied on separate imaging strategies for maximizing sensitivity and specificity[1-12]. TARGET acquires one data set at baseline (pre-contrast), S_0; one early post-contrast, S_1; and one late post-contrast, S_2. The SER index, defined as $(S_1 - S_0) / (S_2 - S_0)$, compares early to late enhancement: SER values less than one indicate breast tissue that enhances gradually; SER values equal to one indicate breast tissue enhancement that is stable between the early and late post-contrast time points; SER values greater than one indicate breast tissue demonstrating uptake with contrast washout by the late time point[13-15]. In the preliminary data provided in our original grant application, we presented results in a group of 25 patients with pathology confirmation. MRI correctly identified carcinoma in 21/25 cases using a two-point comparison only: percent enhancement (PE) = $(S_1 - S_0)/ S_0 > 80\%$. The one false positive was resolved when SER>1.2 was used as an additional criteria for malignancy. Of particular interest, these preliminary studies also suggested a relationship between SER value and tumor grade in the group of 18 invasive carcinomas. The focus of this grant has been to verify these findings in a larger population of patients with confirmed breast carcinoma, and investigate the potential of SER as a non-invasive prognostic marker.

BODY

Experimental Methods, Assumptions and Procedures: 50 women subjects per year are enrolled in this research protocol and receive one breast MRI exam prior to undergoing surgery. Study eligibility include women with highly suspicious breast abnormality or confirmed breast carcinoma on the basis of fine needle aspiration (FNA), core biopsy, excisional biopsy, or lumpectomy with positive margins. The MRI procedure is performed on a General Electric 1.5 Tesla SIGNA scanner using a bilateral phased-array breast radiofrequency coil. The imaging exam consists of a bilateral, axial T1-weighted, spin echo localization scan, a sagittal, fat-suppressed T2-weighted fast spin echo scan of the symptomatic breast only, and contrast-enhanced TARGET series of the symptomatic breast only, using a 3D fat-suppressed, fast gradient echo sequence: TR = 11 ms, TE = 4.2 ms, 20 degree flip angle, 256 x 192 imaging matrix, 16-18 cm field of view, 60 sections, 2 NEX and no phase wrap option. The scan time for each data acquisition is 5.4 minutes, resulting in a three-point temporal sampling of 0, 2.7 and 8.1 minutes. Gadolinium-DTPA is administered intravenously through an indwelling catheter at a dose of 0.1 mmol/kg body weight, following the first scan of the TARGET series.

Software and hardware upgrades to our General Electric Signa scanner over the past three years have allowed us to decrease the TR of the 3D pulse sequence to 8.0 ms, maintaining all other parameters constant. The resulting scan time is 4:36 minutes, resulting in a new temporal sampling of 0, 2 min 18 sec and 6 min 54 sec.

Following each patient exam, MRI data are transferred off-line to a UNIX workstation for processing and analysis. Maximum intensity projections and region-of-interest calculations are performed to measure peak PE and SER values in the area of suspicion based upon the patient's reason for referral. Additional areas of suspicion and incidental MRI findings are also characterized. Tissue tracking and histopathology correlation procedures were developed in Year I and continue to be used in this study.

Results and Discussion:
We have completed patient accrual in our study. Our combined patient database now includes 444 patients. In our Statement of Work, we estimated that Tasks 6 &7 under Specific Aim 1 and Task 3 under Specific Aim 2 would be underway during Year 4. These tasks were as follows:

SPECIFIC AIM 1 (Determine the histologic basis for interpreting SER patterns)
Task 6: Perform remaining patient studies; compile results in accumulated studies.
Task 7: Analyze data

SPECIFIC AIM 2 (Investigate the possible prognostic value of SER characteristics)
Task 3: Perform multi-variate analysis to evaluate prognostic potential.

The analysis of data has resulted in four papers (one published, two accepted and in press, and one submitted) in the last year, as listed below. We also have two papers in preparation that report the results of the application of our techniques to the assessment of tumor response to neoadjuvant chemotherapy.

During the last year, we completed an analysis of the subset of patients diagnosed with ductal carcinoma in situ (DCIS) only, a pre-invasive cancer. In this study we evaluated MRI performance for assessment of residual disease, occult invasion and multi-centric disease in order to determine the clinical role of MRI in the management of preinvasive breast cancers. 51 patients with biopsy-proven DCIS underwent high resolution contrast-enhanced MRI prior to surgical treatment using the TARGET method. MR findings were correlated with mammography and histopathologic findings. Histopathology demonstrated the presence of residual disease in 39 patients. Invasive cancer was associated with DCIS in 7 patients. 16 patients had multicentric disease. The accuracy of MRI was 88% in predicting residual disease, 82% in predicting invasive disease and 90% in predicting multicentricity. Subgroup analysis demonstrated higher performance of MRI when the diagnosis of DCIS was made by core biopsy rather than surgical biopsy. When compared to mammography, the accuracy of MRI was statistically equivalent for the diagnosis of occult invasion. However, for the diagnosis of residual disease and multicentricity, MRI was more sensitive and had a higher negative predictive value than mammography ($p<0.05$). These findings have been reported in a manuscript by Hwang et al., recently submitted for publication to Cancer Research[23].

In the final year of the project period, we have continued to apply the techniques developed in Years 1-3 to the assessment of tumor response to neoadjuvant chemotherapy in patients with locally-advanced breast cancer. A total of 58 patients have been enrolled in the neoadjuvant study; a preliminary analysis of results was performed after 42 patients. A summary of our findings were reported at the 2nd International Congress on MR Mammography held in Jena, Germany in September 2000. An abstract of these results also was published recently in European Radiology[24]. A summary of our findings follows.

All 42 patients underwent MRI before and following a course (4 cycles) of adriamycin/cytoxan (AC) chemotherapy. In 18 patients, MR images were also obtained after one cycle of AC. All patients went on to surgery, however four patients also received an additional regimen of taxol chemotherapy after AC and prior to surgery. MRI was performed using the triple acquisition high spatial resolution method. Tumor vascularity was characterized by the signal enhancement ratio (SER) comparing early to late signal enhancement after injection of gadolinium-DTPA. An automated tumor segmentation method was used to calculate tumor longest dimension (LD), tumor volume, peak SER and SER distribution. Tumors were further classified by their morphologic pattern at initial presentation; morphologic types of enhancement were categorized as either pattern 1: single dominant mass with defined circumference;

pattern 2: infiltrating with irregular borders (nodular or diffuse); pattern 3: patchy enhancement; or pattern 4: septal spreading.

Results

At the time of analysis, 34 of 42 patients had completed treatment and undergone surgery. Mean follow-up was 17 months. Of 9 patients with complete clinical response, 7 showed residual disease at pathology; MRI was in agreement in all 7 cases. Six patients had local recurrence, distant metastasis or had died. For preliminary analysis, size of residual disease on pathology (LD_{path}) and number of positive axillary nodes (N_{ax}) were used as intermediate endpoints. Studies have shown that pathologic response after neoadjuvant chemotherapy predicts survival and tumor size and lymph node status retain predictive value after neoadjuvant therapy[4-5]. Longest diameter by MRI (LD_{MRI}) was found to have a good correlation with LD_{path} ($r^2 = .79$). Percent change in LD_{MRI} with treatment was found to correlate significantly with both pathologic 'response' (classified as <1 cm, 1-2.5 cm, or >2.5 cm residual disease) and N_{ax} ($p = .018$ and .035, respectively, Kruskal-Wallis). 100% of patients with <30% change in LD_{MRI} have recurred compared to 45% of those with >30% change. Change in peak SER value was also significantly less in the group of patients with recurrence (23% vs. 37%, respectively; p=.053).

16 of 34 patients were able to undergo successful breast conservation after chemotherapy, whereas only 2 patients were estimated to be able to have breast conservation prior to therapy. 88% of patients with pattern 1 tumors were able to undergo breast conservation (12/13), compared to 28% (4/14), 0% (0/3) and 0% (0/4) of patients with pattern 2, 3, and 4 tumors, respectively.

Previous Results (Reported in Year 3 Annual Report):

As of October 1998, our current patient database included 386 patients with histopathologic results and includes: patient's reason for referral, clinical data, patient history, results of diagnostic tests (mammography, ultrasound, needle biopsy), MRI and pathology. We have performed retrospective evaluations of the effectiveness of contrast-enhanced MRI in several staging applications. We evaluated the diagnostic accuracy of our imaging technique by developing a diagnostic algorithm combining both dynamic and morphologic features of breast lesions on high spatial resolution MRI. In a retrospective sample of 57 patients with suspicious mammographic or palpable findings at the time of MRI, the temporal pattern of enhancement emerged as the most significant MRI imaging parameter by classification and regression tree (CART) analysis, followed by lesion margin. In the population tested, the diagnostic rule yielded a sensitivity and positive predictive value of 97% each and a specificity and negative predictive value of 96% each. The results of this study were recently published in the American Journal of Roentgenology[21].

We evaluated the influence of time interval between lumpectomy and MRI on the ability of contrast-MRI to diagnose residual disease. 68 patients in our database underwent MRI following lumpectomy with positive margins. Patients were stratified according to time interval between lumpectomy and MRI. Specificity improved with each additional week of delay. A twenty-eight day interval was recommended to gain diagnostic accuracy while minimizing delay to re-excision: sensitivity and specificity were 86% and 38% respectively in 34 patients scheduled within 28 days following surgery (mean 19 days) versus 93% and 70% in 37 patients scheduled between one and four months (mean 42 days) following surgery. These results were presented at the 85th Scientific Assembly and Annual Meeting of the Radiological Society of North America and were recently accepted for publication[22]. A retrospective analysis is currently underway to evaluate the subset of patients who underwent MRI following a diagnosis of ductal carcinoma in situ (DCIS). This study will evaluate the usefulness of MRI for defining the extent of residual disease and predicting the presence of occult invasive disease, in comparison to mammography.

We have extended our studies to the characterization of tumor response to neoadjuvant chemotherapy. We have enrolled 42 patients with stage III/IV breast cancer who were given neoadjuvant chemotherapy prior to surgery. These patients underwent MRI before and following a complete course (4 cycles) of

adriamycin/cytoxan (AC) chemotherapy. In 18 patients, MRI was also performed following the first cycle of chemotherapy to investigate whether early changes measurable by MRI could predict the response at the end of four cycles, or whether there is a correlation between early MRI changes and time to recurrence and survival. Image analysis is performed by the automated method developed under a previous aim of this grant[19]. Retrospective analysis was performed on a group of 128 benign, in-situ and low and high grade invasive carcinomas. Receiver operating characteristic (ROC) curve analysis was used to optimize SER cutoffs for differentiating benign and malignant lesions, in-situ and invasive cancers, and low and high grade invasive tumors. These cutoffs were used to determine SER ranges for automated tumor segmentation as a method for measuring changes with treatment. Quantitative measurements included tumor volume, peak SER and percent distribution of SER ranges. MRI was found to accurately assess the extent of residual disease. Tumor classification by MRI pattern appears to correlate with clinical response and nodal status. MRI may have value for early prediction of end response, recurrence and survival.

Previous Results (from Years 1 and 2):
We performed a study to evaluate the value of low temporal resolution kinetic information gained by the three-time point method of data acquisition. We compared a two-point method considering PE only to a three-point method combining PE and SER thresholds, for sensitivity and specificity. Thresholds were separately optimized in each case using receiver operating characteristic (ROC) curve analysis and requiring a minimum sensitivity of 95%. A specificity increase from 42 to 67% was found using the three-point method, in comparison to the two-point method. These results will be presented at the RSNA in December 1998.

We evaluated the correlation of SER value and grade, and SER value and microvessel density (MVD) in a group of 57 patients with confirmed carcinoma and subsequent surgical pathology confirmation. SER correlation with microvessel density counts (by CD 34 staining) was highly significant, $r = 0.62$ ($p<0.002$). The correlation between SER and grade (by SBR number) was $r = 0.59$ ($p<0.004$). SER increased with the grade of tumor, showing greatest separation between tumors of grade 2 and 3[17-18].

In an evaluation of staging accuracy, tumor extent was measured on MRI and mammography and their concordance with pathology was compared. In a group of 45 patients with carcinoma and MRI and mammography taken at comparable times, carcinoma was correctly identified by MRI in 98% of cases, versus 84% for mammography. True anatomic extent was correctly identified much more often with MRI than with mammography (96% vs. 44%), with the greatest value in cases of multi-focal disease, ductal carcinoma in situ (DCIS), or invasive carcinoma with an extensive intraductal component (EIC)[18].

Key Research Accomplishments during year III:

- One published and two accepted (in press) manuscript resulting from studies funded under this grant (included in Reportable Outcomes).
- Analysis completed of subset of patients with DCIS only. A paper reporting our findings has been submitted to Cancer Research.
- Extension of the techniques developed under this study to the evaluation of neoadjuvant chemotherapy response. This work was invited for presentation at the 2nd International Congress on MR Mammography, held at the Friedrich Schiller University, Jena, Germany in September, 2000. The abstract was published in European Radiology (see citation below). Our work in this area has led to a multi-center trial to evaluate the ability of MRI to measure response and predict survival for patients with stage III breast cancer undergoing neoadjuvant chemotherapy. The study has been approved for funding by the American College of Radiology Imaging Network (ACRIN) and is expected to open in early 2001.

Reportable Outcomes:

- Papers:

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  Esserman LJ, **Hylton NM**, Yassa L, Frankel S and Weidner N. Utility of MRI in the management of breast cancer: evidence for improved preoperative staging. J Clin Oncol, 1999, 17:1:110-119.

  Esserman LJ, **Hylton NM**, George T and Weidner N. Contrast-enhanced magnetic resonance imaging to assess tumor histopathology and angiogenesis in breast cancer. The Breast Journal, 1999; 5:1:13-21.

  Hylton NM. Vascularity assessment of breast lesions with gadolinium-enhanced MR imaging. MRI Clinics of North America, 1999; 7:2:411-420.

  Partridge SC, Heumann EJ, **Hylton NM**. Semi-automated analysis for MRI of breast tumors. Studies in Health Technology and Informatics, 1999, 62:259-260.

  Kinkel K, Helbich TH, Barclay J, Schwerin EH, Esserman LJ, Sickles EA, **Hylton NM**. Dynamic high-spatial-resolution MR imaging of suspicious breast lesions: diagnostic criteria and interobserver variability. Am J Roentgenol. 2000 Jul;175(1):35-43.

  Frei KA, Kinkel K, Bonel HM, Lu Y, Esserman LJ, **Hylton NM**. Performance of breast MRI in patients with positive margins after lumpectomy: influence of time interval between lumpectomy and MR imaging. (in press, AJR)

  Esserman LJ, Kaplan E, Partridge S, Tripathy D, Rugo H, Park J, Hwang S, Kuerer H, Sudilovsky D, Lu Y, **Hylton NM**. MR Imaging phenotype is associated with response to AC neoadjuvant chemotherapy in stage III breast cancer. (in press, Journal of Surgical Oncology)

  Hwang ES, Kinkel K, Esserman LJ, Weidner N, Barclay J, **Hylton NM**. The clinical utility of MRI in patients diagnosed with ductal carcinoma in situ of the breast. (submitted to Cancer Research)

- Abstracts and Presentations:

  Hylton NM, Esserman LJ, Partridge SC, Wang WL, Schwerin E and Sickles E. Increased Diagnostic Specificity of High Resolution Breast MRI Using a Three-Time-Point Method. Proc. 21st Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, 1998.

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Frei KA, Kinkel K, Esserman LJ, **Hylton NM**. Performance of breast MR imaging in patients with positive margins after lumpectomy: influence of time interval between lumpectomy and MR imaging. Radiology 1999, 213(P):1175.

Hylton NM, Partridge S, Heumann E, Tripathy D, Weidner N, Esserman L. Automated Analysis of Tumor Response to Neoadjuvant Chemotherapy with High Resolution MRI. 22nd Annual San Antonio Breast Cancer Symposium. December 8-11, 1999.

Esserman L, Partridge S, Kaplan E, Bainer R, Kuerer H, Tripathy D, Weidner N, **Hylton N**. MRI: A Tool for non-invasive measurement and prediction of response after neoadjuvant chemotherapy in locally advanced breast cancer. 22nd Annual San Antonio Breast Cancer Symposium. December 8-11, 1999.

Partridge SC, McKinnon G, Newitt DC, Day MR, **Hylton NM**. Influence of menstrual phase on apparent diffusion coefficients measured in the breast. 8th Scientific Meeting of the International Society of Magnetic Resonance in Medicine, 2000, 492.

Hylton N, Esserman L, Partridge S, Heumann E, Kaplan E, Beccaria L, Proctor E, Bruce N, Kuerer M, Tripathy D, Sickles E, Weidner N. Evaluation of Neoadjuvant Chemotherapy Response and Prediction of Survival in Locally Advanced Breast Cancer Using Contrast-MRI. 8th Scientific Meeting of the International Society of Magnetic Resonance in Medicine, 2000, 2167.

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Hylton NM, Esserman LJ, Partridge SC, Kaplan E, Lu Y, Sudilovsky D, Kuerer MH, Park J, Tripathy D and Weidner N. Contrast-MRI for Characterization of Tumor Response to Neoadjuvant Chemotherapy and Prediction of Recurrence in Stage III Breast Cancer. European Radiology, 2000, 10:9:F10.

- Funding based on work supported by this award:

ACTIVE:
The Susan G. Komen Breast Cancer Foundation Jan 2000-Dec 2001
'Magnetic Resonance Imaging and Directed Fine Needle Aspiration Biopsy for High Risk Screening and Surveillance'
Principal Investigator: N. Hylton
Total Costs: $248,420.00
Percent Effort: 10%

Study Aim: The goal of this project is to develop and evaluate a magnetic resonance imaging (MRI) screening examination that includes high resolution, fat-suppressed 3D imaging to identify lesions, and MRI-directed fine needle aspiration biopsy (FNAb) to increase diagnostic accuracy.

U.S. Army Medical Research and Materiel Command Oct 1997-Sept 2000
"Improving the Specificity of High Resolution Breast MRI by Optimizing Data Acquisition Techniques and Diagnostic Models"
Principal Investigator: Savannah Partridge
Role on Project (N. Hylton): Faculty Mentor
Percent Effort: 5%
Total Costs: $42,206.00
Study Aim: To develop and optimize new diagnostic models for high resolution 3D contrast MRI of the breast for improved differentiation between benign and malignant breast.

American College of Radiology Imaging Network (ACRIN) 6657 (approved)
April 2001-March 2004
'CONTRAST-ENHANCED BREAST MRI FOR EVALUATION OF PATIENTS UNDERGOING NEOADJUVANT TREATMENT FOR STAGE III BREAST CANCER: A Companion Study To CALGB 49808 Trial Of Neoadjuvant 4AC With Or Without Dexrazoxane Followed By Weekly Paclitaxel With Or Without Herceptin'
Principal Investigator: N. Hylton
Total Costs: $250,000.00
Percent Effort: 5%
Study Aim: Multi-center companion study to the Cancer and Leukemia Group B (CALGB) study 49808, a phase III clinical trial to assess the response of HER-2/neu over-expressing Stage III tumors to chemotherap and Herceptin. ACRIN 6657 will evaluate the ability of contrast-MRI to assess response to neoadjuvant treatment and to predict outcome and survival.

PENDING:
California Breast Cancer Research Program July 2001-June 2003
" Breast Tumor Classification for Measuring Therapy Response"
Principal Investigator: C. Klifa
Total Costs:
Percent Effort: 2%
Study Aim: To develop quantitative image processing techniques for contrast-enhanced breast MRI to classify tumor types and assess response for patients undergoing neoadjuvant chemotherapy.

CONCLUSIONS

Our original aims were to refine our high resolution MR imaging technique for the characterization of breast carcinoma. We studied over 400 patients with confirmed or highly suspected breast cancer and assessed the morphologic and contrast-enhancement properties of a spectrum of breast cancers of varied histologic type, grade and stage. The imaging properties were carefully correlated with histopathologic assessment, and based upon this correlation, we were able to refine our diagnostic criteria and demonstrate a high degree of accuracy for staging disease extent. We retrospectively analyzed the performance of our contrast-MRI for multiple staging applications, including the effects of time delay following lumpectomy on the evaluation of residual disease following MRI, and the usefulness of contrast-MRI in defining residual disease and detecting occult invasion in patients with a biopsy demonstrating DCIS only. We have extended our studies beyond our original goals to include the assessment of tumor response to pre-operative chemotherapy. Our early results suggest that MRI is more accurate than conventional methods (mammography and physical exam) for measuring change with

treatment and may provide unique non-invasive characteristics that can be used to predict response and recurrence. This work has led to the funding of a multi-center study of MRI for assessment of neoadjuvant treatment response for patients with stage III breast cancer.

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